# Local Therapies for Localised Neuropathic Pain

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## Introduction

Localised neuropathic pain commonly arises due to damage to a peripheral nerve; but can also arise from damage to or hyper-reactivity of nerve plexus, nerve root, or occasionally from central processes[1]. This type of pain can cause significant negative impact on quality of life. Systemic drugs used to treat Neuropathic pain, such as antidepressants, anticonvulsants and opioid analgesics can also cause significant side effects such as sedation, drowsiness and cognitive dysfunction that increase difficulties for the patient[2].

This paper will address local treatment options that are effective for localised neuropathic pain whilst avoiding the long-term systemic side effects of medications; it should be mentioned that there are well known complications that could arise after invasive therapies, but these are minimised in the hands of experienced clinicians and by using advanced imaging techniques and other precautionary measures.

## Topical Pharmacological Agents

Amitriptyline and Gabapentin are well known systemic drugs used in the management of neuropathic pain. However, they are also used as topical agents, apparently with some success, particularly the use of gabapentin in vulvodynia. The mechanisms for topical relief of pain seem to differ from their central effects, and the mechanism of action is unknown. The uses of many agents are limited to sympathetically mediated pain[3] and treatment-resistant pain, as they are not freely available, although there are ongoing studies looking into the use of various combinations of different agents topically.

Amitriptyline cream has been used in the management of post-traumatic neuropathic pain[4], but in studies when compared with 5% lidocaine cream[5] and 3.3% doxepin cream[6], amitriptyline cream was found to be less efficacious. However, when combined with ketamine cream, topical amitriptyline showed promising results in neuropathic pain states[7] and also in the management of refractory proctodynia[8]. The use of the above combined with Baclofen in a cream form has been shown to be effective in chemotherapy-induced peripheral neuropathy[9]. Topical Gabapentin has been used in the management of localised and generalised vulvodynia[10] and anecdotally has been tried in other neuropathic pain states. Lidocaine creams and EMLA are also used, especially for mucous membranes, but has largely been replaced by 5% Lidocaine plasters on skin, which is discussed below.

Ketamine is used as a systemic agent in the management of neuropathic pain, but its use as a topical gel has also been explored[11]. It has been used in the management of oral mucositis[12] and its use in combination with amitriptyline cream has been discussed before[7,8,9]. Clonidine is another agent that has been tried topically[13] and it works by blocking the emerging pain signals at peripheral terminals via alpha-2 adrenoceptors without producing undesirable central side effects[14]. GTN spray was also tried with some success in the management of painful diabetic neuropathy either as a sole agent or in combination with anticonvulsants[15].

The agent that is commonly used for localised neuropathic pains including painful diabetic neuropathy and post-herpetic neuralgia is capsaicin[16,17]. It is usually used as a 0.025% or 0.075% cream and is licensed for the management of painful diabetic neuropathy[18,19]. Combination of doxepin and capsaicin cream was found to produce faster results in another study[20]. Some patients find it difficult to be compliant with the treatment due to the burning nature of the cream and it needs to be applied 3-4 times a day for several weeks before producing pain relief. The 8% capsaicin patch, which is a single application could improve on this and is discussed in detail below.

## 5% Lidocaine Plaster

Topical 5% lidocaine plaster has been around since late 1999 and is a topical analgesic, which is recommended by some algorithms as first line therapy for the treatment of localised, peripheral neuropathic pain[21,22]. Each 10 cm x 14 cm plaster contains 700 mg (5%w/w) lidocaine in a white hydrogel plaster containing adhesive material and is applied for a period no longer than 12 hours with a subsequent plaster-free interval for another 12 hours[23]; a maximum of three plasters are used at a time[23]. The application of the plaster over the intact skin of the affected area is usually well-tolerated and application site side effects like erythema, rash and pruritus are mostly self-limiting[24]. Patients need to be followed up after 2-4 weeks and if there is no analgesic benefit in that period, it is unlikely to get more benefit than the barrier effect.

The mechanism of action is still unclear, but the local analgesic effect is by stabilising neuronal membranes, and from animal studies it is thought to down-regulate the sodium channels present in the peripheral nerve endings, reducing ectopic nociceptive pain signal transmission[25]. As a long-term consequence, reduction of peripheral nerve input may counteract central sensitisation. Lidocaine induces a TRPV1 dependent release of CGRP, which is a key component of neurogenic inflammation and long-term topical application

of lidocaine reduces nerve fibre density in the epidermis[26,27]; this degeneration may explain the observed loss of pain[28]. Additionally, the plaster acts as a barrier protecting the skin from mechanical stimuli, which can trigger pain sensations due to allodynia and hyperpathia.

The current licensed indication for 5% lidocaine plaster is for post-herpetic neuralgia[23]. Various studies evaluating the long-term efficacy, safety and tolerability of the lidocaine plaster show consistent and sustained long-term pain relief for up to 24 months and longer[29]. The data further confirms that in newly diagnosed patients, pain relief was achieved at 1 week of treatment and subsequent reductions occurred in the weeks thereafter. 5% lidocaine plasters have also been successfully used in patients with other types of neuropathic pain states, either as a single agent[30] or in combination[31]. Promising results have also been obtained with the use of 5% lidocaine patch for the treatment of mild-to-moderate carpal tunnel syndrome, the efficacy being comparable to that of the more invasive anaesthetic/corticosteroid injection otherwise used[32]. It was found that the plaster was well tolerated by the patients who also reported a low side effect profile.

5% lidocaine plasters are also used in treating other pain conditions including myofascial pain syndrome (MPS), caused by trigger points in muscle or muscle fascia. The existing standard treatment for this is infiltration of the trigger points with local anaesthetic +/- steroids; however this intervention normally can produce some discomfort in the patients. The application of topical 5% lidocaine plasters for the symptoms of MPS was found to be effective and highly acceptable to patients with MPS[33]. The use of 5% lidocaine plasters in three different chronic pain conditions for two weeks also had a significant reduction and impact on all pain measures assessed by neuropathic pain scoring[34]. It has also been shown that 5% lidocaine plaster can be used as an additional therapeutic option in chronic back pain[35] and also showed no statistically significant difference between using the 5% lidocaine plaster versus COX-2 inhibitors in treating osteoarthritis pain[36].

In summary, 5% lidocaine plaster is an effective means of treating ongoing pain and allodynia due to localised neuropathic pain and diverse peripheral neuropathies. The sustained efficacy, combined with its safety and tolerability profile results in a favourable benefit-risk ratio, suggesting its safety for long-term use. However, it is to be noted that, being licensed for post-herpetic neuralgia, the predominant use is still in neuropathic pain and not for musculo-skeletal pain.

**8% Capsaicin Patch**

Capsaicin (8-methy-N-vanillyl-6-nonenamide) is the active component of the chilli pepper and is an agonist of the transient receptor potential vanilloid-1 receptor (TRPV1)[37]. Topical capsaicin creams, 0.025% and 0.075%, have been used over twenty years in the management of peripheral neuropathic pains[38], but tend to have limited analgesic effect, as it needs to be applied up to four times daily for several weeks, which could lead to reduced compliance rates. Some patients also complain of experiencing a burning sensation when using the cream[39]. The low dose topical capsaicin cream may reduce neuropathic pain in PHN but in one trial it failed show efficacy in HIV-associated distal sensory polyneuropathy[40].

A high concentration capsaicin (8%w/w) patch was approved in the UK in 2010 for the treatment of PHN and other peripheral neuropathic states other than diabetic neuropathy. Each 14 cm x 20 cm patch, with a total of 179 mg of capsaicin (640 mcg/cm2) in the silicone-adhesive mixture, is designed to deliver a therapeutic dose of capsaicin during a single application of 30-60 minutes. Capsaicin causes an initial enhanced stimulation of TRPV1-expressing cutaneous nociceptors that may be associated with painful sensations, followed by a reduction in the TRPV1-expressing nociceptors, leading to prolonged analgesia[41]. Over a period of months, there may be a gradual re-emergence of the neuropathy due to nerve fibre re-innervation of the treated area. The mechanism of action is thought to be selective and reversible defunctioning of cutaneous sensory nerve endings expressing TRPV1. However, large myelinated nerve fibres are unaffected, thereby preserving the integrity of protective touch, vibratory and thermal connections[41]. This is important as it means capsaicin treatment can lead to reduction in pain without clinically relevant changes in protective sensation.

Evidence from several controlled clinical trials have demonstrated that applying a single 60 minute high concentration capsaicin patch can significantly reduce neuropathic pain in patients with PHN[42-45]. The studies also confirmed that it could be effective as a monotherapy or in conjunction with other pain analgesia[40,42,43] and more importantly, the pain relief was maintained for up to at least 12 weeks[43-46]. The patch showed greater improvement in mean pain scores at all assessment times[42-46]. A randomised double blind controlled study in patients with PHN for at least three months showed that following treatment with the 8% capsaicin patch, pain scores began declining as early as the end of day 1 and were on average reduced by 36% during the first week[46-47].

Studies have also shown that the 8% capsaicin patch is effective in HIV-associated distal sensory polyneuropathy, a painful condition with limited effective treatments[40,48,49]. A multicentric double blind controlled dose-finding study, which evaluated the safety and efficacy of the 8% patch but studied with different durations of application - 30, 60 or 90 minutes in treating PHN[46]. In summary the authors found that a single topical application of the patch provided pain reduction for up to 3 months[46]. Treatment duration of 60 minutes was found to be the lowest effective dose time and generally well tolerated, but for the treatment of painful HIV neuropathy of the feet, it was found that a 30 minutes application gave similar analgesic effect for a similar duration[48-49].

Side effects of 8% capsaicin are predominantly localised, such as application site pain, pruritus and papules; these responded to localised cooling and analgesics, and lasted only for a few days[45,50]. A transient, but clinically insignificant rise in blood pressure has also been noted during the duration of the patch application and was

self-limiting[45]. Exposure to capsaicin may result in nasopharyngitis and this can be avoided by careful removal, rolling the patch inwards to avoid contact, for safe disposal.

In summary, high dose capsaicin patch is generally well tolerated by patients and appears to have some potential advantages over some of the current first line agents in term of side effect profile. Poor compliance from patients for capsaicin cream is avoided, as the whole therapeutic dose is delivered during a single supervised application.

**Percutaneous Electrical Nerve Stimulation Therapy (PENS)**

PENS therapy is a type of minimally invasive peripheral nerve stimulation used in the treatment of chronic peripheral neuropathic pain. Since the advent of the "Gate Control Theory" of pain[51], electrical stimulation has been used to provide analgesia. Pain due to nociceptive stimuli is carried via C-fibres to the dorsal horn at laminar 1 & 2 and then onwards via the spinothalamic tract to terminate in the sensory cortex. Transcutaneous Electrical Nerve Stimulation (TENS) causes a reduction of pain by stimulating peripheral inhibitory fibres. This may not always be effective in some neuropathic pain states, as C-fibre termination at laminae 1 & 2 ceases as a result of peripheral nerve damage and is replaced by Aβ-fibres at the lamina[52]. The Aβ-fibres projecting into the lamina can cause an exaggerated nociceptive response to what are normally innocuous stimuli[53] and hence these patients may not tolerate TENS, but may be more likely to benefit from PENS therapy. PENS uses a frequency-dependent electrical current (usually 2 Hz and 100 Hz alternating every 3 seconds), to modulate the activity of peripheral nerves and can be used to stimulate a single peripheral nerve[54] or the most peripheral branches of a peripheral nerve as field stimulation[55]. The electrical current is delivered through a 21gauge disposable probe of varying lengths of 20 mm to 200 mm inserted percutaneously to target the affected area for a period of 25 minutes.

PENS therapy offers patients the potential for intermediate relief and ongoing management of chronic peripheral neuropathic pain conditions like scar pain including post-thoracotomy, post-mastectomy and post-hernia repair pains[56]. It has also been used with success in intractable cluster headaches[57] and occipital neuralgias[58]. PENS gives good analgesic results in patients with post-irradiation allodynia and following trigeminal field neuropathy following head and neck cancer surgery and radiotherapy[59]. These patients reported improved quality of life and could make a significant reduction in opioid analgesia and also systemic neuropathic pain agents[60].

PENS therapy is contraindicated in the presence of demand type cardiac pacemakers and patient refusal. Caution is to be exercised in patients known to have heart disease, epilepsy, on anticoagulants and in pregnancy. PENS therapy is best deferred when there is local or systemic infection or coagulopathy. Possible adverse events may include temporary flare of pain, bleeding or haematoma at probe insertion site, and the possibility of infection at the probe entry point; misplacement of the probe may cause temporary neuropraxia, though this is very rare.

PENS can be used as a diagnostic therapy to identify patients who are likely to benefit from a permanently implanted neurostimulator and could reduce the incidence of patients who fail to benefit from a lengthy, potentially traumatic and costly procedure61. Distinguishing patients who may stand to benefit from permanently implantable neurostimulation devices, from those who may not, and the ability to recognise those who will gain an enhanced quality of life through ongoing PENS therapy, offers clear clinical and economic advantages when considered in conjunction with other neurostimulation therapies. It has also been used with success in patients with focal neuropathic pain in patients with cancer who require frequent MRI scans which make an implantable neurostimulator contraindicated[60].

PENS offers the option of a minimally invasive neuromodulation therapy that can be carried out in a procedure room, either as a diagnostic tool prior to implantable stimulators or a continuing treatment option for localised neuropathic pain states. It is associated with a low risk profile and is a cost-effective option when pharmacological options are either ineffective or when the effective dose causes unacceptable side effects to the patient that could significantly impact on their quality of life. The evidence base for PENS treatment is growing, but are currently limited to case series and case reports; there needs to be carefully conducted randomised controlled clinical trials (RCTs) to further validate and provide hard evidence of therapeutic efficacy.

**Radiofrequency Ablation**

Radiofrequency techniques have been in use for more than 30 years in the management of chronic pain conditions[62], particularly back[63] and neck pain and also neuropathic conditions like trigeminal neuralgia and other refractory neuropathic pain states[64]. There is a wealth of clinical experience and success in the use of both conventional (thermal) and pulsed radiofrequency techniques, including several large case series, but there are only a few high quality randomised controlled trials to validate these results[65]. However, it is widely used in clinical practice in the management of focal neuropathic pain[66].

The principles and procedure of radiofrequency have been well established and both conventional and pulsed lesioning are used in common practice[67,68]. Conventional radiofrequency using a thermal lesion at temperatures higher than 65 degrees Celsius can produce significant damage to neural tissue; pulsed lesioning is done at lower temperatures around 42 degrees Celsius and thus gives rise to minimal damage and hence a lower incidence of complications[69]. Experimental studies have shown that though no gross change is seen on both treatments, electron microscopic examination has revealed minimal disruption of the myelin envelope of the axon[70], indicating that the analgesic effect of radiofrequency technique is not just by causing a thermal lesion. Pulsed radiofrequency defines an electromagnetic field in the vicinity of a lesion, modifying neuro-cellular function with minimal cellular destruction[71]. The mechanisms of the analgesic action by pulsed radiofrequency by the enhancement of descending nor-adrenergic and serotonergic

systems[72] have also been described in animal studies. There may also be an anti-nociceptive effect produced simply due to radiofrequency application[73].

The use of radiofrequency lesioning for trigeminal neuralgia has been in practice for nearly forty years[74]; the technique is well described[75] and studies have shown that conventional radiofrequency is far more effective in sustaining analgesia than pulsed lesioning[76]. Percutaneous radiofrequency rhizotomy has been effective in idiopathic trigeminal neuralgia, symptomatic facial pain and herpes zoster of the fifth cranial nerve, but not effective in atypical facial pain[77]. It has been the recommended option for treating trigeminal pain in the elderly, but microvascular decompression remains the first line choice for younger patients[78]. The procedure is not without complications and apart from pain and bruising, major complications such as other cranial nerve palsies[79], subarachnoid haemmorhage[80] and rhinorrheoa[81] have also been reported. Targeting the sphenopalatine ganglion[82], particularly using advanced imaging including CT-guidance[83] and virtual reality techniques[84] has higher efficacy and reduced risk of complications. Radiofrequency neurolysis of the infra-orbital nerve has been done when trigeminal ganglion or posterior root ablation is contraindicated[85]. Pulsed radiofrequency has been used in the treatment of occipital neuralgia with the pain improving substantially in more than half the number of patients[86,87].

Several other neuropathic pain conditions have been treated with radiofrequency with good to exceptional results as reported in case series. Pulsed radiofrequency of the lateral cutaneous nerve of the thigh has been used in successfully treating meralgia paraesthetica[88]. It has also been used with success in managing groin pain and orchialgia[89] and also refractory pudendal neuralgia[90]. There are case reports of effective radiofrequency lesioning for obturator nerve neuropathy[91] for conditions such as hip arthritis. The effects of producing a radiofrequency lesion adjacent to the dorsal root ganglion in patients with thoracic segmental pain has also been reported, with 67% of patients reporting pain relief at 8 weeks and half the patients having relief at 36 weeks[92]. More recently it has been shown that pulsed radiofrequency of the dorsal root ganglion is superior to pharmacotherapy or pulsed radiofrequency of the intercostal nerves in the treatment of chronic postsurgical thoracic pain[93]. There are also case reports of CT-guided dorsal root ganglion thermocoagulation for treating post herpetic neuralgia, where the majority of patients had excellent pain relief and others had a decrease in symptoms[94]. Radiofrequency lesioning of the thoracic paravertebral nerve for refractory neuropathic pain following breast cancer surgery has also been reported[95].

There are several case reports and case series regarding the use of radiofrequency ablation in the management of lower limb phantom pain, including pulsed radiofrequency of the sciatic nerve[96]. The patients reported improved prosthetic tolerance and reduction of oral analgesic medications. The analgesic effect is thought to be due to inhibition of evoked synaptic activity[97]. It has also been reported that there could be increased pain, new pain syndromes and also abnormal sweating in the limb stump[98]. Pulsed radiofrequency has also been used in treating myofascial trigger points and scar neuromas with 67% of the patients reporting pain relief lasting between 6 to 12 weeks[99]. It has also been used in treating patients with chronic neuropathic spinal pain after failed conservative management[100]. A 12-year long-term retrospective analysis of using radiofrequency application to areas of pain in the treatment of neurogenic heel pain has shown a high success rate with few associated risks and less post-operative morbidity[101]. Radiofrequency ablation has been used with success for the management of prolonged moderate to severe heel pain associated with plantar fasciitis[102].

Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome (CRPS) has poor evidence in literature due to lack of large well-designed studies[103]. However, radiofrequency lesions of the stellate ganglion have been used with success in CRPS Type 2, ischaemic pain, cervicobrachialgia and post-thoracotomy pain[104]. Pulsed radiofrequency lumbar sympatholysis has also been used in the management of CRPS in a patient with spinal injury[105]. However, the evidence base for the use of radiofrequency ablation for these conditions has not yet been validated by randomised controlled trials[106].

**Summary**

Topical agents such as 5% Lidocaine plasters, 8% Capsaicin patch and procedures lsuch as PENS Therapy give the added option of delivering pain relief locally without the side-effects of systemic drugs for localised neuropathic pain. Though radiofrequency techniques are widely used and there is moderate evidence for facet joint neurotomy, more well-designed studies need to be conducted to gather more evidence in its use in other neuropathic pain states.

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